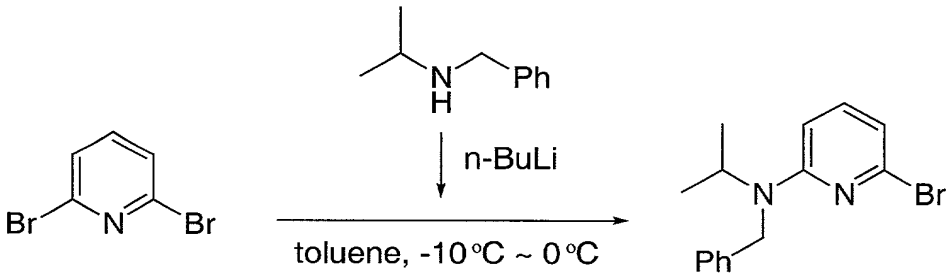
EXAMPLE 4

Mono-amination of 2,6-Dibromopyridine (6)



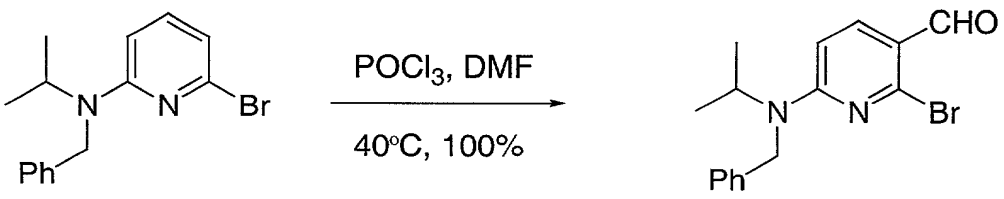
6 **7**

n-BuLi (1.27L, 2.5M, 3.18mol) is added to a solution of *N*-isopropylbenzylamine (473g, 3.17mol) in 0.67L toluene and 0.72L hexane at -15°C to -10°C for about two hours. The mixture is aged at -10°C to 0°C for 0.5 hour to give the lithium amide. It is then transferred into a slurry of 2,6-dibromipyridine (500g, 2.11mol) and *N*-isopropylbenzylamine (317g, 2.11mol, 1.0 equiv.) in toluene (2.5L) and hexane (2.5L) at 5°C to 10°C for about an hour. The mixture is stirred at 0°C until the reaction is completed as monitored by HPLC. The reaction is quenched by transferring the reaction mixture via a cannula into 2N HCl (2.5L) at 10°C to 20°C with vigorous stirring. The flask is rinsed with hexane. About 1.5L of DMF is added to dissolve most of the dark precipitates. The mixture is stirred for 20 minutes. The layers are separated, and then the organic layer is washed with a mixture of 3:1 DMF:water and water. It is concentrated under vacuum (100 to 40 mmHg, 40°C bath) to a minimum volume, flushed with toluene (40 to 20mmHg, 40°C~50°C bath), and then pumped for two hours to give the crude product **7** (596g, 93.3w%, 86% yield). ^{1}H NMR indicated 5.7w% toluene. HPLC indicated 2.7A% toluene, 0.8A% bis-amination product and 94.4A% of the desired product **7**.

HPLC conditions: Zorbax SB-C8 4.6 x 250 mm; MeCN 40-90% in 15 min; 1.50mL/min, 10mM Trizma buffer (pH=7); 30°C, UV detection at 220nm; Retention times (min): 2,6-dibromopyridine **6** (5.8), *N*-isopropylbenzylamine (5.1, broad); toluene (6.7), 2-(*N*-isopropylbenzylamino)-6-bromopyridine **7** (12.6), and bisamination (16.7).

EXAMPLE 5

Formylation

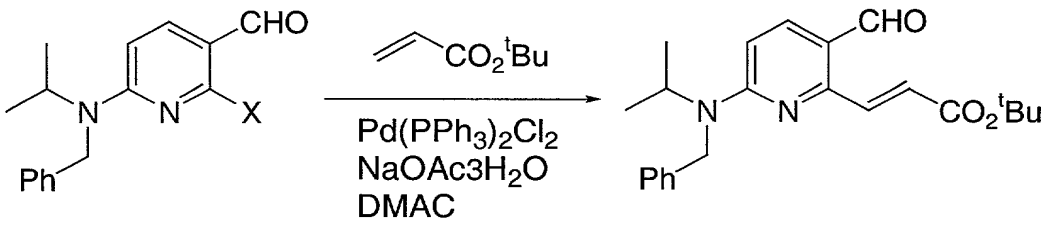


7 **8**

A solution of crude 2-(*N*-isopropylbenzylamino)-6-bromopyridine **7** (550g, 93.3w%, 1.68mol) in DMF (2.8 L) is cooled to 10°C, and then $POCl_3$ (670mL, 1.10Kg, 7.2mol, 4.3 equiv.) is added by using a dropping funnel while maintaining the batch temperature below 30°C for about 1.2 hours. The mixture is heated to about 40°C and then aged overnight for about 15 hours. Once the reaction is completed, the reaction mixture is cooled to below 20°C and cannulated into a mixture of water and toluene with vigorous stirring and ice-water cooling to maintain <20°C for about two hours. After separating the layers, the aqueous DMF layer is extracted with more toluene. The combined toluene layer is washed with water and then treated with Darco-KB (50g) for about 0.5 hour. The mixture is then filtered through a Solka-Floc pad and the filter pad is washed with toluene. The filtrate is concentrated under vacuum (about 40°C~50°C bath, 30-50mmHg), and the residue is pumped under high vacuum overnight to give the crude product **8** as a brown oil (570g, 102% yield uncorrected for purity).

EXAMPLE 6

Heck Reaction:



8 **9**

A 2L three-neck round bottom flask equipped with a mechanical stirrer, temperature probe, and nitrogen inlet is charged with a degassed solution of bromoaldehyde **8** in dimethylacetamide. The reaction is purged with nitrogen for about 20 minutes. Both sodium acetate trihydrate ($NaOAc \cdot 3H_2O$) and t-butyl acrylate are added to the solution. Finally the Pd catalyst is added to the reaction vessel, and the vessel is flushed with nitrogen. The resulting mixture is stirred mechanically for about 9 hours at 80°C. When the reaction is completed, the solution is cooled to room temperature, diluted with toluene (7.5ml/g of starting material) and filtered through solka floc. The solka floc is then washed with 2.5ml/g of toluene. The solution is washed once with water. The organic layer is azeotroped with toluene, and the material is taken into the next step at a final volume of 620mL.

HPLC Conditions: Waters Symmetry C8, 4.6mmx250mm; TSP UV2000 dual wavelength, 1AU/volt output; Acetonitrile; 45°C; 1.5ml/min.; UV detection at 220nm; Retention times (min.): aldehyde **8** (X = Br, 10.8; X = Cl, 10.3), cis Heck isomer (11.2), and trans Heck isomer (13.4).